

in a previous article.⁵ Here we shall confine ourselves to one aspect of it, an aspect for which the family doctor is particularly well placed. The family relationships of the anxiety neurotic are likely to be unhealthy, and here the family doctor's tactful attention can be invaluable. A deft touch is required: any radical change in family relationships will probably be resisted and it could make matters worse. But it may help to encourage, for instance, the overdependent housewife to be a

little more self-sufficient; to suggest to the husband who has taken over his wife's domain while she has been ill that he now relinquish it; or to urge the husband who becomes drunk and jealous on a Saturday night to abstain, or, if he appears incapable of modifying his behaviour, to refer him for treatment.

(Part III, with a list of references and suggestions for further reading, will be printed next week.)

TODAY'S DRUGS

With the help of expert contributors we print in this section notes on drugs in current use.

Vitamin D

Vitamin D is the name given to a group of steroid compounds which possess antirachitic properties. The most potent of these is vitamin D₃ (cholecalciferol); the most commonly used in clinical medicine are vitamin D₂ (calciferol) and dihydrotachysterol. There is no vitamin D₁—what was so called was later shown to be a mixture of compounds.

Pharmacology

Vitamin D₂ and vitamin D₃ are derived from the conversion by ultraviolet light of provitamins which themselves do not possess antirachitic activity. Ultraviolet light irradiation of a number of steroids will result in the cleavage of the carbon-carbon bond between C₉ and C₁₀ of the steroid structure; this is an essential step in the development of antirachitic activity. The provitamin of vitamin D₂ (ergosterol) is of vegetable origin and is found in yeast, fungi, and ergot; after irradiation ergosterol yields vitamin D₂ and tachysterol, a reduction product of which is dihydrotachysterol. The provitamin of vitamin D₃ (7-dehydrocholesterol) is of animal origin; it is found in the Malpighian layer of the epidermis, in fish liver oils, and in milk. The antirachitic properties of vitamin D₂ and vitamin D₃ differ among the species; in man there is little difference between them, but in general vitamin D₃ has greater antirachitic activity than vitamin D₂.

Vitamin D is fat soluble and requires the presence of bile acids for absorption from the gut. Normally vitamin D is readily absorbed from the intestine, mostly in the upper part of the small gut (especially the mid-jejunum), and it is then transported with chylomicrons into the lymphatics. The intestinal absorption of Vitamin D is reduced in patients with certain liver diseases, in patients with intestinal malabsorption, and in the presence of large amounts of mineral oil (liquid paraffin). About half of an oral dose of the vitamin is excreted via the bile into the faeces; minimal amounts appear in the urine. After intravenous administration about half of the dose is found in the liver, where it remains for several hours; lesser amounts are present in plasma bound to globulin and to albumin, in bone and the kidney (proximal convoluted tubules), and in the intestine and muscle. Once absorbed vitamin D undergoes conversion into a number of metabolites; some of these possess antirachitic properties and others do not. The most potent of these active metabolites so far discovered is 25-hydroxycholecalciferol, which has 1.4 times the antirachitic activity of the parent vitamin D₃ and which acts upon the target tissues at greater speed.

Actions of Vitamin D

Vitamin D exerts effects on many tissues of the body, but the principal sites of action are the gut, bone, and kidney. The major effects of the vitamin are on calcium and phosphorus metabolism. The intestinal absorption, the mobilization from bone, and the renal excretion of these minerals are all increased by the vitamin; the general effect is to increase the serum calcium concentration. There is a time lag of 12 to 24 hours between the administration of the vitamin and the initiation of these actions. The effects of vitamin D on the gut and other tissues are mediated through changes in protein metabolism; they are blocked by inhibitors of protein synthesis (actinomycin D). The time lag in the response to vitamin D is probably accounted for by the time taken to stimulate new protein synthesis and by the time taken for the conversion of the vitamin into more active compounds.

Vitamin D is closely interrelated with the actions of parathyroid hormone; and the vitamin appears to play a permissive part in the action of the hormone on bone.

Requirements and Sources

The normal requirements of vitamin D are not known with certainty. There is no doubt that in the past they were greatly overestimated, particularly in the case of children, in whom overdosage led to the serious complication of hypercalcaemia. The amount of the vitamin required varies with age and is influenced by pregnancy and lactation. A mean daily intake of 10 microgrammes (400 units) will prevent rickets in childhood, and this amount is probably adequate during pregnancy and lactation; smaller amounts (2–5 µg.) are probably sufficient for adults.

The ability of the skin to synthesize vitamin D is related to the duration of exposure to ultraviolet light and to the degree of pigmentation of the skin; coloured peoples are less sensitive to the effects of ultraviolet rays than are those with fair skin. Little vitamin D is made in the skin of city dwellers, and natural foods, with the exception of certain fish and eggs, contain little or no vitamin D. The major sources are foods fortified with vitamin D (milk in the U.S.A.; National dried milk and infant cereals; margarine) and cod-liver and halibut-liver oils.

Clinical Indications for Vitamin D

The only therapeutic indications for vitamin D are in the prevention of rickets in childhood, in the treatment of established rickets and osteomalacia, and in the management of hypoparathyroidism.

The curative dose of vitamin D in rickets and osteomalacia depends upon the underlying cause of the disorder. In deprivational rickets and osteomalacia 10–100 μ g. a day will promote healing of bone lesions. Rickets and osteomalacia sometimes develop in patients with intestinal malabsorption syndromes, with liver disease, and with renal disorders, even though their dietary intake of vitamin D is adequate. In these patients treatment of the primary disease is important; in patients in whom this is not possible (chronic renal failure; renal tubular disorders) much larger doses of vitamin D (1 to 10 mg. daily) may be required; in some instances the vitamin has to be given parenterally. In these patients receiving large doses of vitamin D a satisfactory response must be judged clinically, and they require careful supervision. Once the bones have healed it is often possible to maintain the patient on a smaller dose.

Hypoparathyroidism is most commonly found as a sequel to subtotal thyroidectomy. In this condition parathyroid hormone secretion fails, and there is a reduced mobilization of calcium from bone; this leads to hypocalcaemia. Treatment is aimed at restoring the serum calcium concentration to normal or low normal levels. Dihydroxycholesterol has often been used successfully in the management of this condition, but this compound has little advantage over vitamin D₂ and is considerably more expensive. Both cause an increase in the serum calcium concentration through an increase in bone resorption. Vitamin D₂ is effective in most cases and should be the drug of first choice. The usual starting dose varies from 1.25–5 mg., and this is given for the first two or three days; then the dose should be reduced rapidly to a maintenance level of 1–2 mg. daily. Some cases may require larger doses than this. Opinions differ about the need for a calcium supplement; a dietary intake of 500 to 1,000 mg. should be aimed at, and this can be provided easily with milk.

Toxicity

Vitamin D is excreted and metabolized slowly, and for these reasons the maximum effect of a given dose may not become apparent for four to eight weeks. Patients also vary in their sensitivity to the vitamin. Frequent changes in the dose of vitamin D are contraindicated. Poisoning with vitamin D readily occurs in patients receiving a milligram or more a day. Overdosage with vitamin D is an important and serious complication of treatment; it produces hypercalcaemia and renal failure, which may be irreversible. Lassitude, anorexia, thirst, nausea, and vomiting are common symptoms; and psychoses, major convulsions, and coma may be features. All patients at risk should be warned of the significance of these symptoms. Treatment comprises withdrawal of the vitamin, correction of water and electrolyte disturbances, and the administration of cortisone; in some cases sodium sulphate may be needed to combat the hypercalcaemia. The importance of strict clinical supervision and frequent determinations of the serum calcium concentration in patients receiving large doses of vitamin D cannot be overemphasized.

B.M.J. Publications

The following are available from the Publishing Manager, B.M.A. House, Tavistock Square, London W.C.1. The prices include postage.

<i>The New General Practice</i> ...	Price 16s.
<i>B.M.J. Cumulative Index, 1967</i> ...	Price 30s.
(15s. to B.M.A. members)	
<i>Porphyria—a Royal Malady</i> ...	Price 13s. 6d.
<i>Is There an Alternative?</i> ...	Price 7s. 6d.
<i>Treatment of Common Skin Diseases</i>	Price 10s.
<i>Charles Hastings and Worcester</i> ...	Price 3s. 6d.

ANY QUESTIONS?

We publish below a selection of questions and answers of general interest.

Oral Contraceptives and Raynaud's Disease

Q.—*Are oral contraceptives contraindicated in women who suffer from Raynaud's disease? If so, what preparation may be given to such patients to postpone menstruation at the time of their wedding?*

A.—I know of no contraindication to the use of steroid hormones, including oral contraceptives, in women who suffer from Raynaud's disease.

The request to postpone menstruation at the time of a wedding is one which is often made. If the girl is seen three months or more before the wedding and wishes to take oral contraceptives in any case it is reasonable to start her on them right away, and by adjusting the dose—that is, by giving the product for a shorter or longer period—to bring menstruation at a time that will not coincide with the wedding date. If it is merely intended to postpone menstruation to cover the date of the wedding, and contraceptives are not being given, the best product would be norethisterone acetate (Primolut N. Schering) 5 mg. three times a day. This should start three days before menstruation is expected, and should be continued for five to seven days. One cannot guarantee that

breakthrough bleeding will not take place, but it is probable that menstruation will be postponed or not occur until two to three days after the cessation of treatment. This dosage can also be added on to the end of a course of an oral contraceptive with the similar object of postponing the onset of menstruation.

Addiction to Bronchodilator Aerosols

Q.—*What is the treatment for a 16-year-old girl with mild asthma who has become addicted to an isoprenaline spray?*

A.—There have been many reports in the past few years of deaths in asthma due to overdosage of bronchodilator aerosols. Two recent papers^{1,2} have documented the recent increase in mortality from asthma and pointed out a possible association with bronchodilator aerosols. These aerosols are undoubtedly effective in relieving airways obstruction, so that patients easily become dependent on them and in an emergency overdose themselves.

If the patient's addiction is really because she needs the aerosol to breathe adequately

it may be she should be receiving other treatment such as steroids. In a girl aged 16 there may be psychological factors, and she may be addicted to using a spray rather than to its isoprenaline content. It might be worth trying the effect of an aerosol containing the inert propellant only. Alternatively, a better way might be to try disodium cromoglycate. It is a dry powder inhaled through a "spinaler." This treatment would have the advantage of giving an antiallergy agent and one which was taken by inhalation.

REFERENCES

- Speizer, F. E., Doll, R., and Heaf, P., *Brit. med. J.*, 1968, **1**, 335.
- Speizer, F. E., Doll, R., Heaf, P., and Strang, L. B., *Brit. med. J.*, 1968, **1**, 339.

Chronic Parotitis

Q.—*Can a chronic, recurring parotitis in an adult be due to mumps?*

A.—A chronic recurring parotitis in an adult cannot be due to mumps. A patient with chronic parotitis should always be investigated for evidence of tuberculosis, sarcoidosis, or leukaemia. When the condition is recurrent the most likely cause is obstruction in the parotid duct.